12 yo Girl with Neurofibromatosis Type 1 and Rapid Pubertal Progression

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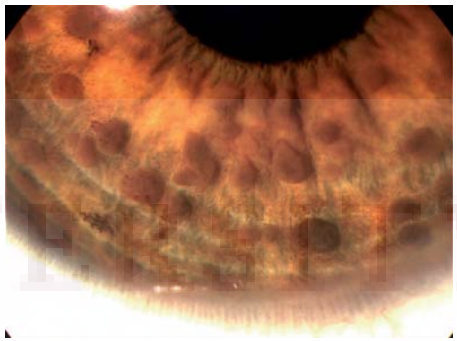
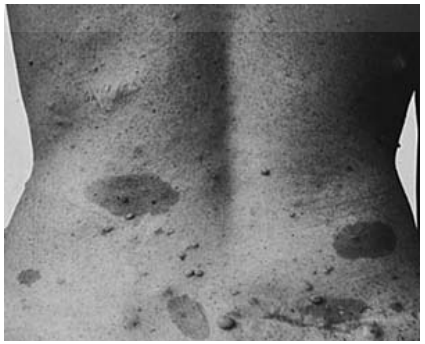
Initial Visit

- 12-2/12 yo girl with NF-1 and chronic renal insufficiency s/p cadaveric renal transplant referred for short stature
- Diagnosed with NF-1 at age 7 months due to café-au-lait macules. Mother was then diagnosed with NF-1
- Has worn the same pants size for 3 years, shoe size changes once yearly

Neurofibromatosis Type 1

- Mutation of *NF1* gene on Chromo 17q11.2 that encodes Neurofibromin
- Incidence ~ 1:3000
- 50% familial (autosomal dominant), 50% sporadic
- Penetrance nearly 100%, highly variable expressivity
- Most common endocrine disorder: precocious puberty





NIH diagnostic criteria for neurofibromatosis type 1

Two or more of the following clinical features must be present:
Six or more café au lait macules of more than 5 mm in greatest diameter in prepubertal individuals, and more than 15 mm in greatest diameter in postpubertal individuals.
Two or more neurofibromas of any type or one plexiform neurofibroma
Freckling in the axillary or inguinal regions
Optic glioma
Two or more iris hamartoma (Lisch nodules)
Distinctive bony lesion such as sphenoid dysplasia, or thinning of the long bone cortex with or without pseudoarthrosis
A first-degree relative (parent, sibling, or offspring) with NF 1 based on the above criteria.

UpToDate

PMH

- Born at 36 weeks, wt: 1st%, lt: 33rd%
- Age 9 months
  - Cardiac arrest, myocarditis, dilated cardiomyopathy and HTN
  - Evaluation for HTN revealed abdominal aortic artery and bilateral renal artery stenosis
  - Renal artery stents were placed
- Age 18 months
  - Right renal artery bypass x 2
  - Left nephrectomy
  - Path: intimal fibromuscular hyperplasia consistent with NF-1
- Age 2 years:
  - Right nephrectomy with cadaveric renal transplant

PMH

- Age 3 years:
  - Acute → chronic rejection
- 2010
  - Last MRI: subtle “bright objects” in bilateral thalami and left internal capsule c/w NF-1
- Currently
  - Receives chronic immunosuppressant therapy
  - Baseline Cr 1.9-2.3
  - Chronic anemia, HTN

ROS

- Constitutional: poor appetite and weight gain
- HEENT: Lisch nodules, no visual disturbances
- CV: HTN, renovascular fibromas
- Resp: negative
- GI: no constipation
- GU: No menses, possible breast tissue
- MSK: leg and knee pain at night
- Skin: Few cutaneous fibromas, many café-au-lait macules
- Neuro: No focal deficits, abnormal EEG of uncertain clinical significance
- Psych: insomina, anxiety, mood swings
- Development: significant learning difficulties

PMH

Meds

- CellCept 200 mg po BID
- Tacrolimus 2 mg po BID
- Clonazepam 0.5 mg po BID
- Prednisone 5 mg po daily (HC equivalent ~20mg/m2/day)
- Darbepoetin alfa 25 mcg SC q7 days
- Ferrous sulfate 325 mg po TID
- Labetalol 100 mg po BID
- Lasix 20 mg daily
- Pepcid 20mg daily
- Calcium acetate 667 mg BID
- Bactrim 1 tab daily

Social History

- Lives with her mother and sister
- Her father is not involved
- Attends the 6th grade and receives tutoring
- Refuses counseling

Family History

- Mother
  - NF-1, cutaneous lesions
  - 64 inches tall, menarche age 13 years
- Father
  - Healthy
  - 67 inches tall
- NF-1: sister, MGM, maternal aunts
- Maternal cousin 4’9”
- No pubertal delay or advancement

P.E.

Wt: 26.5kg (5 kg < 3rd%), Wt age : 8.5 yrs, Ht: 121.6cm (-4 SD), Ht age: 7 years, BMI 17.9 kg/m2 (46th%)

- Constitutional: short, thin, normal body proportions
- HEENT: Round, chubby face, PERRLA, Lisch nodules, OP clear
- Neck: no thyromegaly
- CV: RRR, no murmurs, 2+ periph pulses
- Resp: Lungs CTAB, normal effort, Tanner I breasts
- GI: mass consistent with kidney in right abdomen, multiple healed surgical scars
- GU: Several Tanner II hairs on the mons pubis
- MSK: slight genu varum, no scoliosis
- Skin: Few cutaneous fibromas, café-au-lait macules, axillary freckling, Tanner I axillary hair
- Neuro: CN grossly intact bilaterally, 2+ patellar DTRs

Evaluation

- Prepubertal with multiple risk factors for poor growth
- BMP: 137/4.5/102/22/24/2 Glu 111 Ca 9.5 AP 89
- Hb 9.9 Hct 30.2
- IGF-1 540 ng/mL (143-693)
- IGF-BP3 6.8 mcg/mL (1.4-5.2)
- TSH 1.25 mcU/mL (0.9-1.7)
- free T4 1.23 ng/dL (0.3-4)
- Bone Age: 7 y 6-11 mo at CA 12 y 2 mo; predicted adult height 60-60.75 inches (MPH 63 inches)

Diagnosis & Treatment

- Extreme short stature due to poor wt gain/appetite, renal insufficiency, chronic glucocorticoid use, anemia
- Cannot rule-out GH deficiency
- Felt GH was contraindicated given vascular neurofibromas
- Encouraged improved nutrition, will follow through transplantation
- GnRH agonist therapy if puberty begins prior to transplant

3 months later

- New breast development, no galactorrhea
- Increased pubic hair growth, no menses
- Placed on renal transplant list for chronic rejection (Cr 1.9-2.3)
- No change in immunosuppressant therapy
- On Exam:
  - Ht: 121.7 cm (up 0.1 cm)
  - Tanner III breasts, few strands of Tanner III pubic hair, on mons pubis and intralabialy

IMPRESSIONS/CONCERNS?

Differential Diagnosis

- Normal pubertal timing
- Premature thelarche and adrenarche (based on BA)
- Central precocious puberty
  - NF-1-related (hypothalamic harmatoma, optic glioma)
  - Idiopathic
- Ovarian Cyst
- Estrogen-secreting tumor
- Prolactinemia (renal insufficiency)

Evaluation

- Performed at 1738
  - LH 8 mIU/mL (prepubertal< 0.2)
  - FSH 6.1 mIU/mL (prepubertal < 2.7)
  - Estradiol 43 pg/mL (prepubertal 2-14)
  - DHEAS < 15 ug/dL
  - HbA1c 5.2%
- Consistent with gonadotropin-dependent puberty
- Concerned for extreme short stature if left untreated
- Recommend GnRH agonist
  - Family preferred Lupron 11.25 mg q 28 days

2 months later

- Lupron was not approved
- Continued breast enlargement, increased pubic hair growth
- No menses
- On exam:
  - Ht: 122.3 cm, annualized growth velocity 2.88 cm/yr over 2 mo
  - Tanner IV breasts, minimal tenderness, no galactorrhea
  - Slight increase in Tanner III pubic hair
- Plan:
  - Start Lupron
  - MRI brain and pituitary
  - Bone age

Clinical Questions

- Can growth hormone be used safely in pateints with NF-1?
- What is the incidence and mechanism of precocious puberty in patients with NF-1?
- What is the natural history of growth and puberty in patients with NF-1?

GH & Risk for Malignancy in NF-1

- Retrospective study of 102 children with NF-1 (ages 6-13 yrs) treated with GH
- 43 had intracranial tumor, 30 with optic pathway tumors
- Max f/u duration was 3 years
- 12 pts had precocious puberty
- Those with tumors entered puberty early than those without
- Similar optic glioma progression/recurrence rates reported in other studies

Table IV. Adverse events

Adverse event	No. of patients
Progression of NF	
Increasing size of café-au-lait patches	9
New neurofibromas	4
Increased size of pre-lumbar mass (?neurofibroma)	1
Recurrence of optic glioma	2
New intracranial tumor	
Right cerebral hemisphere astrocytoma	1
Pilocytic astrocytoma (?site)	1
Brainstem glioma	2
Other (gastroenteritis, allergies, chest infection)	19

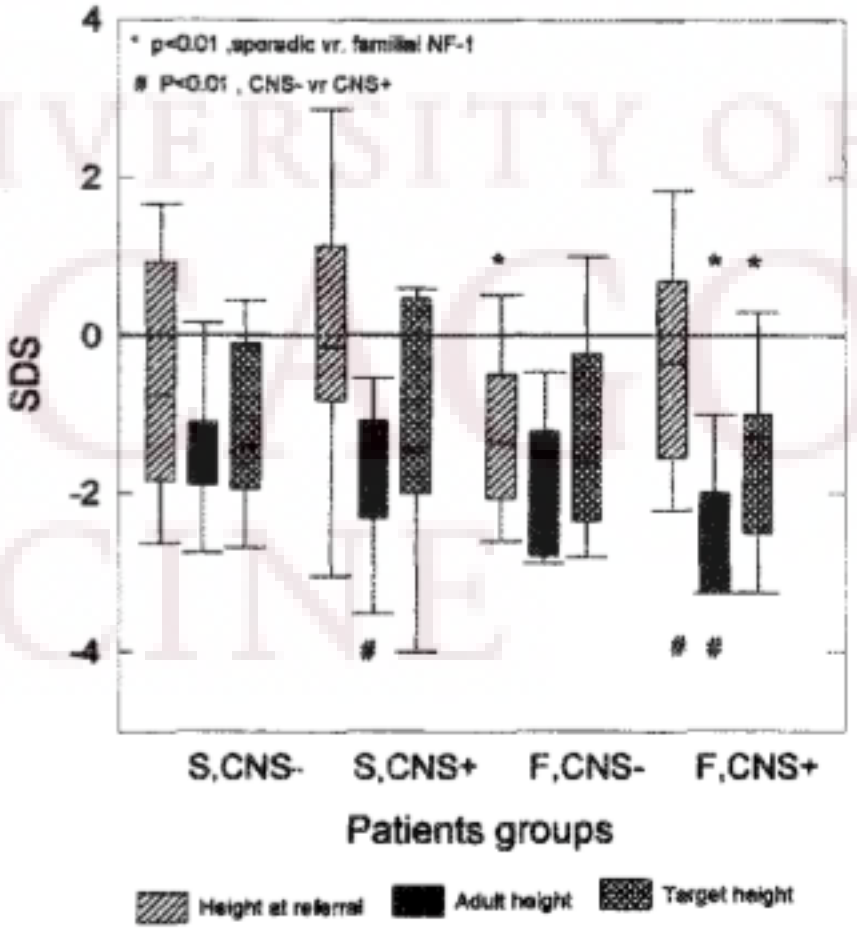
Howell et al. 1998 J Pediatr; 133 :201-5

Central Precocious Puberty & NF-1

- Habiby et al 1995
  - 7/219 (3%) children with NF-1 had central precocious puberty
  - All 7 had optic pathway tumors (39% of those with OPTs)
  - Male:female ratio 5:2 for CPP
- Virdis et al 2000
  - 31/412 children with NF-1 had OPTs, 10/412 (2.4%) had PP, 7/31 (~23%) children with OPTs had CPP
- Case report of 5 yo girl and 8 yo boy with CPP without OPTs

Growth, Puberty & Endocrine Function in Patients with NF-1

- Longitudinal study (mean f/u 8.5 yrs) of 55 boys & 34 girls, sporadic or familial NF-1
- CNS path found in 23/89
  - 3/23 were given GH and T4
  - 5/23 had precocious puberty treated with GnRH agonists
- Precocious Puberty
  - More common in familial cases
  - All 5 had CNS pathology
  - 4/5 were girls
- Growth
  - Short stature in 25.5%, prepubertal
  - Gradual reduction in relative ht for age during puberty
  - 12/28 were short during puberty, only 6 attainted adult ht near target ht
  - Those with CNS path or familial NF-1 with affected father were more like to be short



Carmi et al. *Pediatrics* 1999: 103(6); 1257-62.

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